Remarks

Claims 26-28 are pending in the application. Claims 1-4, 7-9, 12-16, 18, 20, and 23-25 have been canceled without prejudice. Claim 26 has been amended to remove "micelle forming agents" and "polymeric carriers." Therefore, no new matter has been added. Moreover, the claim amendments and cancelations should not be construed to be an acquiescence to any of the claim rejections. Rather, the amendments and cancelations to the claims are being made solely to expedite the prosecution of the above-identified application. The Applicants expressly reserve the right to further prosecute the same or similar claims in subsequent patent applications claiming the benefit of priority to the instant application. 35 USC § 120.

Claim Rejections Based on 35 USC § 112¶1

Claims 1-4, 7-9, 12-16, 18, 20, and 23-28 were rejected under 35 USC § 112¶1, based on the Examiner's contention that "the specification, while being enabling for fentanyl in combination with cyclodextrins, does not reasonably provide enablement for multitudes of compounds falling within the scope of the formula A in combination with micelle forming carriers and polymeric carriers."

In order to expedite prosecution, the Applicants have canceled claims 1-4, 7-9, 12-16, 8, 20, and 23-25. In addition, claim 26 was amended to remove "micelle forming agents" and "polymeric carriers" from the Markush group defining the excipient. The Applicants point out that cyclodextrins are oligomers, not polymeric carriers. Therefore, removal of the term "polymeric carriers" from claim 26 does not alter the scope of protection sought for cyclodextrins.

The Applicants contend that the Application as filed provides sufficient enablement for amended claim 26 and claims that depend on claim 26. In regards to the Examiner's comment that the "specification provides no guidance at all as to how the multitudes of compounds [that fall within the scope of formula A] are synthesized," the Applicants remind the Examiner that the compounds that fall within the scope of formula A are derivatives of fentanyl, a known compound. One of ordinary skill in the relevant art, namely an individual with a Ph.D. in

Remarks

Claims 26-28 are pending in the application. Claims 1-4, 7-9, 12-16, 18, 20, and 23-25 have been canceled without prejudice. Claim 26 has been amended to remove "micelle forming agents" and "polymeric carriers." Therefore, no new matter has been added. Moreover, the claim amendments and cancelations should not be construed to be an acquiescence to any of the claim rejections. Rather, the amendments and cancelations to the claims are being made solely to expedite the prosecution of the above-identified application. The Applicants expressly reserve the right to further prosecute the same or similar claims in subsequent patent applications claiming the benefit of priority to the instant application. 35 USC § 120.

Claim Rejections Based on 35 USC § 112¶1

Claims 1-4, 7-9, 12-16, 18, 20, and 23-28 were rejected under 35 USC § 112¶1, based on the Examiner's contention that "the specification, while being enabling for fentanyl in combination with cyclodextrins, does not reasonably provide enablement for multitudes of compounds falling within the scope of the formula A in combination with micelle forming carriers and polymeric carriers."

In order to expedite prosecution, the Applicants have canceled claims 1-4, 7-9, 12-16, 8, 20, and 23-25. In addition, claim 26 was amended to remove "micelle forming agents" and "polymeric carriers" from the Markush group defining the excipient. The Applicants point out that cyclodextrins are oligomers, not polymeric carriers. Therefore, removal of the term "polymeric carriers" from claim 26 does not alter the scope of protection sought for cyclodextrins.

The Applicants contend that the Application as filed provides sufficient enablement for amended claim 26 and claims that depend on claim 26. In regards to the Examiner's comment that the "specification provides no guidance at all as to how the multitudes of compounds [that fall within the scope of formula A] are synthesized," the Applicants remind the Examiner that the compounds that fall within the scope of formula A are derivatives of fentanyl, a known compound. One of ordinary skill in the relevant art, namely an individual with a Ph.D. in

The Applicants respectfully rebut the *prima facie* case of obviousness based on WO 92/02256 because secondary considerations of long-felt need and unexpected results establish that claims 26-28 are not obvious in light of WO 92/02256.

First, the Applicants point out that it is commonly recognized by those of ordinary skill in the art of drug delivery that oral administration of a medicinal agent is preferred. A few of the advantages of oral adminstration over other forms of administration are presented below. Oral administration allows the patient to administer the therapeutic agent while at home and without the assistance of others. For example, pharmaceutical formulations administered by injection often must be given by a trained medical professional. In many instances, this requires the patient to travel to a doctor's office or hospital to receive the treatment. This form of administration is particularly undesirable when the patient requires multiple injections each day. In addition, oral administration of a medicinal agent does not cause any of the pain or discomfort often associated with administration by injection. Oral administration is often preferred for children that are fearful of receiving an injection. Oral administration can also be advantageous to transdermal delivery of a medicinal agent. Transdermal delivery requires the patient to wear a patch on the skin which contains the medicinal agent. Patients may be reluctant to wear the patch because it is uncomfortable or not asthetically pleasing. In addition, the patch may accidentally fall off without the patient's knowledge, preventing the patient from receiving the needed medication. Oral administration of a medicinal agent does not suffer from these drawbacks because the medicinal agent is ingested, not worn on the surface of the body.

Second, the Applicants point out that fentanyl has been known since the 1960s; and there is a large market for fentanyl-based analgesics. As described in the application, there are millions of people that suffer from pain which could potentially be treated using fentanyl. Thus, there is ample need for orally-bioavailable formulations of fentanyl. However, the Applicants are aware of only one FDA-approved product for oral administration of fentanyl. ACTIQ® is an oral transmucosal formulation of fentanyl citrate. <www.actiq.com>. However, this formulation is known to cause nausea, vomiting, and/or a burning sensation in the mouth which are clearly undesirable side effects; moreover, in certain instances the formulation "did not yield analgesia greater than placebo...." *See* Shaiova et al. in *Support Care Cancer* **2004**, *12*, 268 (abstract of the publication reproduced below).

BACKGROUND: Oral transmucosal fentanyl citrate (OTFC; ACTIQ) incorporates fentanyl into a lozenge allowing drug delivery through the oral mucosa resulting in rapid pain relief. OTFC is effective for breakthrough pain and could be particularly useful in patients with mucositis. METHODS: This randomized, double-blind, crossover study assessed two formulations of OTFC for tolerability in 14 patients with radiation-induced mucositis. On four separate days, patients with grade 3 or 4 mucositis received an OTFC unit 45 min before radiation treatment. Two units had a sweetened matrix formulation and two had a compressed powder formulation. One unit of each formulation contained 200 microg fentanyl and one was placebo. Tolerability, mucositis pain, and formulation preference were evaluated. Changes in oral mucosa were recorded. RESULTS: Both formulations of OTFC were well tolerated. There were no significant differences between formulations in tolerability, patient preference, or VAS pain scores. No changes in oral mucosa were noted. Common treatment-related adverse events included a burning sensation in the mouth, nausea, and vomiting. CONCLUSIONS: Both formulations of OTFC are well tolerated. The presence of fentanyl in either the sweetened matrix or the compressed powder did not alter tolerability or safety. The dose of fentanyl tested did not yield analgesia greater than placebo; future studies of OTFC efficacy in mucositis should evaluate higher doses than 200 microg.

Because oral-delivery methods are generally recognized to be superior, fentanyl formulations have been known since the 1960s, and there is only one known oral formulation for fentanyl, the Applicants contend that a long-felt need exists for oral formulations of fentanyl. Importantly, the present invention fulfills the long-felt need for a fentanyl formulation that can be administered orally. The Applicants respectfully remind the Examiner that a long-felt need is one of the secondary considerations that must be considered in a determination of obviousness. *See* MPEP § 2141. Moreover, the fact that only one FDA-approved product for oral administration of fentanyl exists, despite the need and long history of fentanyl, lends support to the notion that it not obvious to those of skill in the art how to prepare formulations of fentanyl for oral administration.

Third, the Applicants point out that the formulation comprising fentanyl and 10% hydroxypropyl-β-cyclodextrin worked unexpectedly better than the saline formulation of fentanyl in male Sprague-Dawley rats as disclosed in Example 1 of the instant application. For example, the 10% hydroxypropyl-β-cyclodextrin fentanyl formulation gave greater than two-fold

improvement in the tail-flick assay 15 minutes after administration of the fentanyl formulation as compared to the saline formulation of fentanyl. The fast-acting analgesic effect is important because fast-acting pain relief is needed in many applications, such as pain relief needed to treat a patient involved in an accident, trauma, or suffering from a cancer that causes great pain.

Furthermore, the Applicants contend that one of ordinary skill in the art would have no reasonable expectation that addition of a cyclodextrin to fentanyl would give rise to such a substantial improvement in analgesic affect. The Applicants emphasize that pharmaceutical formulations administered orally must endure very different conditions and must overcome different challenges compared to formulations that are injected. For example, orally administered formulations must be stable to the strongly acid conditions of the stomach and the multitude of degradative enzymes located in the intestinal tract. In addition, orally administered fentanyl must be absorbed through the intestinal wall and travel through the circulatory system in order to reach the appropriate receptor to initiate the pain relief. Thus, one of ordinary skill in the art would have no reason to believe that a pharmaceutical compostion that works for injection would work for oral delivery of the same pharmaceutical agent, and in particular, one would not have any reason to expect the same pharmaceutical formulation to work well for oral administration. The Applicants respectfully remind the Examiner that unexpected results is one of the secondary considerations that must be considered in a determination of obviousness. See § MPEP 2141.

Finally, the Applicants contend that claims 26-28 are not obvious because the present invention fulfills a long-felt need for oral formulations of fentanyl. Moreover, the cyclodextrin/fentanyl formulations of the invention work unexpectedly well as analgesic formulations for oral administration. The Applicants respectfully assert that these secondary condsiderations persuasively rebut the Examiner's *prima facie* case of obviousness. The Applicants respectfully remind the Examiner that "the ultimate determination of patentability must be based on consideration of the entire record, by a prepoonderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence." *See* MPEP 716.01(d); and *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 26-28 under 35 USC 103(a) based on WO 92/02256.

In regards to the Examiner's comment that "it is unclear to the Examiner from the results on page 45 (Table) as to how one can come to any conclusion that orally administered fentanyl is effective since the comparison between saline control and the HPCD formulations show a wide variation," the Applicants point out that the different response factors for β-HPCD and γ-HPCD in Table 1 illustrate that β-HPCD and γ-HPCD both provide better pain relief than a saline formulation of fentanyl. Moreover, the differences between the formulations including β-HPCD and γ-HPCD render each of them well-suited to a particular type of pain treatment. The fentanyl formulation comprising β-HPCD produced a 2.5-fold better analagesic effect compared to a fentanyl/saline control 15 minutes after administration, and a 2.7-fold better analagesic effect 30 minutes after adminstration. As noted above, fast-acting pain relief is important in many medical applications, e.g., breakthrough cancer pain. Whereas, the fentanyl formulation comprising γ-HPCD produced a 3.4-fold better analagesic effect compared to a fentanyl/saline control 30 minutes after administration and a 2.0-fold better analagesic effect 45 minutes after adminstration. The analgesia profile for the γ-HPCD/fentanyl formulation indicates it would be well-suited for longer-lasting pain relief. Thus, fentanyl formuations comprising β-HPCD and γ-HPCD yield a better analgesic effect than saline solutions of fentanyl. The different response factors for β-HPCD and γ-HPCD simply illustrate that each could be used advantageously for specific types of pain treatment. In fact, the differences in response factor further support the nonobviousness of the claimed invention.

3. Claims 1-4, 7-9, 12-16, 18, 20, and 23-28 were rejected under 35 USC 103(a), based on the Examiner's contention that they are unpatentable over WO 99/36071. The Examiner states that the WO 99/36071 reference "discloses fentanyl and fentanyl derivatives in polymeric carriers." As described above, the Applicants have amended claim 26 to remove the term "polymeric carriers" and canceled claims 1-4, 7-9, 12-16, 18, 20, and 23-25 in order to expedite prosecution. Moreover, as the Examiner concedes, the teachings of WO 99/36071 lack the claim limitation of oral administration. Consequently, the Applicants contend that WO 99/36071 does not form the basis of a proper *prima facie* case of obviousness because WO 99/36071 does not teach the limitations of claim 26 that the excipient is a cyclodextrin and that administration is oral; in order to form the basis of a proper rejection under 35 USC 103(a), WO 99/36071 must teach all the limitations of the rejected claims. *See In re Zurko*, 111 F.3d 887, 888-889, 42

USPQ 2d 1476, 1478 (Fed. Cir. 1997). Accordingly, WO 99/36071 does not render claims 26-28 unpatentable.

4. Claims 1-4, 7-9, 12-16, 18, 20, and 23-28 were rejected under 35 USC 103(a), based on the Examiner's contention that they are unpatentable over WO 00/47203. The Examiner states that the WO 00/47203 reference "teaches formulations containing narcotic analgesics such as fentanyl in combination with hydroxypropyl-beta cyclodextrin for oral administration." Furthermore, the Examiner contends that "it would have been obvious to one of ordinary skill in the art to use any fentanyl based compounds with a reasonable expectation of success.

In order to expedite prosecution, as described above, claims 1-4, 7-9, 12-16, 18, 20, and 23-25 have been canceled. Regarding claims 26-28, the Applicants contend that claims 26-28 are not obvious because the invention satisfies a long-felt need and works unexpectedly well at causing analgesia. The long-felt need and unexpected results are secondary considerations which outweigh the Examiner's proposed case of obviousness for claims 26-28. The facts surrounding the long-felt need and unexpected results are described at length above in the section relating to WO 92/02256. Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 26-28 under 35 USC 103(a) based on WO 00/47203.

5. Claims 23-28 were rejected under 35 USC 103(a), based on the Examiner's contention that they are unpatentable over WO 92/02256 or WO 99/36071 in view of Farrar et al. (JNCI, 1998), Portenoy et al. (Pain, 1999), and Stanley et al. (Anesth. Analg. 1989). The Examiner states that the Farrar, Portenoy, and Stanley references each teach the efficacy of fentanyl when administered orally. Furthermore, the Examiner contends that "oral administration of the compositions of fentanyl based compounds, with a reasonable expectation of success would have been obvious to one of ordinary skill in the [art] since the references of Farrar et al., Porenoy et al., [and] Stanley et al. show the efficacy of orally administered fentanyl."

As described above, claims 23-25 have been canceled and claim 26 has been amended to remove polymeric carriers in order to expedite prosecution. The Applicants contend that claims 26-28 are not obvious because the invention satisfies a long-felt need and works unexpectedly well at causing analgesia. The long-felt need and unexpected results are secondary considerations which outweigh the Examiner's proposed case of obviousness for claims 26-28.

The facts surrounding the long-felt need and unexpected results are described at length above in the section relating to WO 92/02256. Accordingly, the Applicants respectfully request the withdrawal of the rejections of claims 26-28 under 35 USC 103(a) based on WO 92/02256 or WO 99/36071 in view of Farrar et al (JNCI, 1998), Portenoy et al. (Pain, 1999), and Stanley et al. (Anesth. Analg. 1989).

Fees

The Applicants believe they have provided for all required fees in connection with the filing of this paper. Nevertheless, the Director is hereby authorized to credit any overpayment or charge any required fee to our Deposit Account, **06-1448**.

Conclusion

In view of the above amendments and remarks, it is believed that the pending claims are in condition for allowance. The Applicants respectfully request reconsideration and withdrawal of the pending rejections. The Applicants thank the Examiner for careful consideration of the present case. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to contact the undersigned.

Respectfully submitted,
FOLEY HOAG LLP

Dana Gordon

Dana M. Gordon, Ph.D.
Registration No. 44,719
Attorney for Applicants

Patent Group
FOLEY HOAG LLP
155 Seaport Boulevard
Boston, MA 02210

(617) 832-1000
(617) 832-7000 (FAX)

Date: 6/18/04